American Journal of Industrial Medicine 26:155–169 (1994)

# Occupational Exposure to Chlorinated Aliphatic Hydrocarbons and Risk of Astrocytic Brain Cancer

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Chlorinated aliphatic hydrocarbons (CAHs) were evaluated as potential risk factors for astrocytic brain tumors. Job-exposure matrices for six individual CAHs and for the general class of organic solvents were applied to data from a case-control study of brain cancer among white men. The matrices indicated whether the CAHs were likely to have been used in each industry and occupation by decade (1920–1980), and provided estimates of probability and intensity of exposure for "exposed" industries and occupations. Cumulative exposure indices were calculated for each subject.

Associations of astrocytic brain cancer were observed with likely exposure to carbon tetrachloride, methylene chloride, tetrachloroethylene, and trichloroethylene, but were strongest for methylene chloride. Exposure to chloroform or methyl chloroform showed little indication of an association with brain cancer. Risk of astrocytic brain tumors increased with probability and average intensity of exposure, and with duration of employment in jobs considered exposed to methylene chloride, but not with a cumulative exposure score. These trends could not be explained by exposures to the other solvents. 

**Key words: brain cancer, glioma, solvents, methylene chloride, tetrachloroethylene**

## INTRODUCTION

The age-adjusted mortality rate for cancer of the brain and central nervous system increased steadily in both sexes in the United States from 1950 through the 1980s [Pickle et al., 1987; Hankey et al., 1993]. This trend was primarily due to increases in the oldest age groups [Hankey et al., 1993; McKay et al., 1982]. In white

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Accepted for publication September 5, 1993.

men, who are the subject of this study, tumors of astrocytic origin are the most common histologic type [Ries et al., 1991; Thomas and Waxweiler, 1986; Cordier et al., 1988; Preston-Martin et al., 1989; Burch et al., 1987; Moss, 1985; Olin et al., 1987; Musicco et al., 1982]. Improvement in diagnosis may be responsible for some of the apparent increase, but is unlikely to be the sole factor [Thomas and Waxweiler, 1986; Desmeules et al., 1992].

Brain cancer has been linked to a variety of occupations, many of which have in common exposure to organic solvents [Thomas and Waxweiler, 1986; Cordier et al., 1988; Preston-Martin et al., 1989; Park et al., 1990]. Parental exposure to chlorinated solvents has been reported as a risk factor for brain tumors in children [Peters et al., 1981]. Brain cancer mortality was positively correlated with the concentration of halomethanes in the drinking water of 76 U.S. counties [Cantor et al., 1978]. However, few epidemiologic studies have evaluated the potential carcinogenicity of specific chlorinated aliphatic hydrocarbons (CAHs) [Preston-Martin et al., 1989; Park et al., 1990; Axelson, 1980; Blair, 1980; Blair et al., 1990; Hearne et al., 1987, 1990; Lanes et al., 1990; Norman and Fraumeni, 1981]. Typically they have been based on small populations with relatively little power to detect elevated risks [Axelson, 1980; Blair et al., 1990; Hearne et al., 1987, 1990; Lanes et al., 1990]. The results, although not consistent, suggest that some of these compounds may be carcinogenic.

A case-control study of astrocytic brain tumors in Louisiana, New Jersey, and Pennsylvania uncovered an excess among workers in jobs related to the production and repair of electronic equipment [Thomas et al., 1987b], which appeared to be associated with exposure to solvents. In order to explore further the potential association of brain cancer with specific solvents, we developed job-exposure matrices for six CAHs [Gomez et al., 1994]—carbon tetrachloride, chloroform (trichloromethane), methylene chloride (dichloromethane), methyl chloroform (1,1,1-trichloroethane), tetrachloroethylene (perchloroethylene), and trichloroethylene—and for all organic solvents as a group. The six specific substances were chosen because they have demonstrated mutagenic or carcinogenic effects and have the widest industrial uses among 17 CAHs recently reviewed by the International Agency for Research on Cancer [IARC, 1979, 1986, 1987]. The matrices then were applied to work histories from this study [Thomas et al., 1987b] to evaluate the role of CAHs in the etiology of astrocytic brain cancer. This new exposure assessment afforded us the opportunity to disentangle effects of specific solvents not considered in the previous analyses of these data.

## MATERIALS AND METHODS

### Study Population

Data employed in this study were originally collected to evaluate the hypothesis of an association between work in the chemical and petrochemical industries and risk of brain tumor [Thomas et al., 1986, 1987a,b]. Death certificates were obtained for 741 white men who died of brain or other central nervous system tumors (ICD-9 codes 191, 192, 225, 239.7) during the period January 1, 1978 to June 30, 1980 in southern Louisiana, and January 1, 1979 to December 31, 1981 in northern New Jersey and Philadelphia, Pennsylvania. These areas had been selected because a high proportion of the workforce was employed in the petroleum refining and chemical

manufacturing industries. An equal number of controls was randomly selected from white male residents who died of causes other than brain tumor, cerebrovascular diseases (ICD-9 codes 430–438), epilepsy (ICD-9 code 345), suicide, and homicide. Controls were frequency matched to cases by age, year of death, and study area.

Next-of-kin were successfully located for 654 (88%) cases and 612 (83%) controls. Trained interviewers, unaware of the cause of death of the study subject, administered a standardized questionnaire to the next-of-kin after obtaining informed consent. Occupational information collected on each job held since age 15 included job title, a brief description of tasks, name and location of the company or organization, type of industry, kinds of products, employment dates, and hours worked per week. Information on other possible risk factors for brain cancer was collected.

Among the 483 cases with completed interviews (74% of traced next-of-kin), a hospital diagnosis of astrocytic brain tumor (astrocytoma, glioblastoma, mixed glioma with astrocytic cells) was reported for 300 individuals. Two hundred twenty-nine cases had been pathologically confirmed, while the remaining 71 cases were diagnosed as glioblastoma multiforme or astrocytoma based on appearance by computerized tomography [Thomas et al., 1986, 1987a]. Of their matched controls who completed the interview (n = 386, 63%), 66 were excluded due to a possible association between their cause of death and occupational exposure to CAHs (lung cancer, n = 39; liver cancer, n = 6; leukemia, n = 4; Hodgkin's disease, n = 5; non-Hodgkin's lymphoma, n = 4; and cirrhosis of the liver, n = 8) [Axelson, 1980; Blair, 1980; Blair et al., 1989, 1990; Hardin, 1954; Thiele et al., 1982]. The final data set thus consisted of 300 cases and 320 controls.

## Exposure Assessment

Occupational histories of study subjects were coded using four-digit Standard Industrial Classification codes [Technical Committee on Industrial Classification, 1972] and four-digit Standard Occupational Classification (SOC) codes [U.S. Department of Commerce, 1977]. Special codes were developed for a small number of occupations to capture unique exposure-related information (e.g., anesthesiologist) [Gomez et al., 1994]. Work histories were linked by these codes to job-exposure matrices which characterized likely exposures to the six chlorinated hydrocarbons and to organic solvents [Gomez et al., 1994].

To develop the matrices, the investigators first identified the industries and occupations considered to entail potential exposure to each of the six CAHs, based on data from the literature, unpublished industrial hygiene reports and inspections, and personal judgment of the project industrial hygienists [Gomez et al., 1994]. Each industry and occupation was assigned a semiquantitative estimate (none, low, medium, high) of probability and of intensity of exposure to each substance. Probability was conceptualized as the likelihood that the substance was used by a worker in that industry or occupation. Intensity was an amalgam of expected level of exposure and frequency of use. Scores were relative rankings for each substance and were not comparable quantitatively across CAHs. Because use of CAHs has changed over time, each industry and occupation was assigned positive or zero decade indicators (exposed, unexposed) for each CAH, according to the likely use of the substance during each decade between 1920 and 1980. The matrices thus indicate whether exposure was likely to occur by calendar period, and the probability and intensity of exposure for each industry and each occupation separately.

A matrix for organic solvents as a group was developed to allow an evaluation of the effects of this more general exposure category. For each occupation, the exposure assignments for all organic solvents were generated from assignments for the CAHs, because the six specific CAHs largely covered the range of occupations exposed to organic solvents. Probability or intensity of exposure to organic solvents was the maximum probability score or intensity score, respectively, assigned to any of the six individual agents. High probability of exposure to organic solvents also was assigned to any occupation which was considered exposed with medium probability to three or more of the CAHs. In contrast, for each industry, assignments of probability and of intensity of exposure to organic solvents were developed independently from assignments in the six CAH matrices. No decade indicators of exposure were used in the organic solvent matrix, because organic solvents generally have been used in these occupations and industries over the entire period of 1920–1980, with changes only in the specific compounds used.

The matrices were then linked to the work histories of study subjects. Estimates of probability and intensity of exposure were assigned to each industry-occupation combination in subjects' work histories through the use of an algorithm [Gomez et al., 1994]. These estimates were based on occupation alone, industry alone, or both occupation and industry, depending on the specificity of the exposure environment that could be inferred from the occupational (SOC) code. For example, a printer would be assigned the same probability and level of exposure to a given CAH irrespective of the industry in which he was employed; assignments of probability and intensity therefore were derived wholly from occupation. In contrast, for managers and assemblers, assignments of probability and intensity depended on both occupation and industry.

Several measures summarized subjects' likely exposure histories. Subjects' overall probability of exposure to each substance was defined as the highest probability score for that substance among all their jobs. For each substance, subjects were assigned three surrogates of dose: duration of employment in occupation/industry combinations considered exposed (hereafter called exposed jobs), a cumulative exposure score, and "average" intensity of exposure. The cumulative exposure score for each subject was calculated as a weighted sum of years in all exposed jobs, with weights based on the square of the intensity of exposure (low = 1, medium = 2, and high = 3) assigned to each job [Gomez et al., 1994]. Average intensity was calculated over all exposed jobs for each subject, regardless of probability, based on the same scores without squaring, weighted by duration of employment in each job. In addition, we calculated odds ratios (OR) for specific categories of intensity of exposure (e.g., ever or 20+ years at high intensity, ever or 20+ years at medium intensity with no high intensity jobs) to avoid the use of weights. These categories excluded duration in jobs with lower intensity for subjects with high or medium intensity jobs.

The "ever exposed" category for any specific chemical comprised all subjects employed in an occupation/industry combination classified as exposed, including those whose duration of employment was unavailable. For analyses by duration, subjects whose total duration of employment in an exposed job was unknown, or was less than or equal to 1 year, were dropped from the analysis. Cumulative exposure scores were divided into three categories (low, medium, high), based approximately on tertiles of scores among controls. For each substance, the unexposed were subjects

considered to have no exposure to that substance in any of their jobs. Numbers of subjects classified as exposed are different from those presented in a previous analysis of these data [Thomas et al., 1987a] because of different exposure assessment approaches.

### Statistical Analysis

Maximum likelihood estimates of the OR and 95% confidence intervals (CI) were calculated according to Gart [1970], with adjustment for age (<50, 50–64, 65–79, 80+) and study area. The statistical significance of linear trends (one-sided test) was evaluated using the method of Mantel [1963]. Stratified analysis was inefficient in disentangling the effects of individual solvents due to small numbers of subjects considered exposed to only one CAH. Therefore, logistic regression [Kleinbaum et al., 1982] was used to evaluate simultaneously the effects of the CAHs, controlling for age, study area, and employment in electronics-related occupations or industries (which had been associated with an excess risk of astrocytic brain tumors in a previous analysis [Thomas et al., 1987b]). (Exposure to electromagnetic fields per se was not specifically assessed or considered in the analyses.) Latency was considered by lagging exposure by 10 or 20 years, that is, by disregarding all jobs within 10 or 20 years of death, respectively.

## RESULTS

Astrocytic brain cancer was not significantly associated with "ever" being exposed to organic solvents or to any of the six specific CAHs (Table I). However, risk increased significantly with probability of exposure to organic solvents and to methylene chloride. The 2.4-fold risk among those assigned a high probability of exposure to methylene chloride was of borderline statistical significance. Risk of brain tumor was greater than two for men judged to have medium probability of exposure to carbon tetrachloride, chloroform, and methyl chloroform, but only the first was statistically significant, and trends were not observed with probability of exposure.

Among all probabilities combined, risk increased with duration in jobs considered exposed for both the general category of organic solvents, and for all six CAHs, to varying degrees (Table I). The trends for organic solvents and methyl chloroform were statistically significant. For organic solvents, carbon tetrachloride, and chloroform, the risk increases were due primarily to subjects with medium probability of exposure. In contrast, among subjects judged to have high probability of exposure to methylene chloride, risk increased significantly with duration to sixfold. Although risk estimates rose sharply with duration among men with high probability of exposure to tetrachloroethylene and trichloroethylene, they were based on small numbers, and the trends were not statistically significant.

In analyses in which exposure was lagged by 10 years, relative risks and trends by duration were similar to results presented in Table I (not shown). With a 20-year lag, very few study subjects were exposed more than 20 years to any individual solvent, especially in specific probability categories. For organic solvents, lagging of exposure by 20 years resulted in higher risks and a sharper increase with duration than without consideration of latency (all probabilities: 2–20 years, OR = 1.3 [95% CI: 0.9–2.0]; 21+ years, OR = 2.0 [1.1–3.7]; p for trend = .006; high probability:

**TABLE I. Risk of Astrocytic Brain Cancer by Probability and Duration of Exposure to Organic Solvents and Six Specific CAHs, Controlling for Age and Study Area***

| | | | | | | Duration of employment in exposed jobs | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Ever exposed | | | | 2–20 years | | | | 21+ years | | | | Chi for |
| Substance | Probability | ca | co | OR | 95% CI | ca | co | OR | 95% CI | ca | co | OR | 95% CI | trend |
| Organic | Unexposed | 114 | 142 | 1.0 | | | | | | | | | | |
| solvents | Low | 48 | 56 | 1.1 | (0.6–1.7) | 28 | 28 | 1.2 | (0.6–2.2) | 16 | 15 | 1.5 | (0.6–3.5) | 1.20 |
| | Medium | 32 | 28 | 1.5 | (0.8–2.7) | 9 | 13 | 0.8 | (0.3–2.1) | 22 | 12 | 2.6 | (1.1–5.9) | 2.07[a] |
| | High | 106 | 94 | 1.4 | (0.9–2.1) | 43 | 44 | 1.2 | (0.7–2.0) | 49 | 42 | 1.5 | (0.9–2.5) | 1.50 |
| | All | 186 | 178 | 1.3 | (0.9–1.8) | 80 | 85 | 1.1 | (0.7–1.7) | 87 | 69 | 1.7 | (1.1–2.6) | 2.35[b] |
| Chi for trend | | | | 1.93[a] | | | | | | | | | | |
| Carbon | Unexposed | 170 | 198 | 1.0 | | | | | | | | | | |
| tetrachloride | Low | 104 | 101 | 1.2 | (0.8–1.7) | 63 | 62 | 1.1 | (0.7–1.8) | 27 | 24 | 1.4 | (0.8–2.8) | 1.25 |
| | Medium | 13 | 4 | 3.6 | (1.1–13.7) | 6 | 3 | 2.1 | (0.4–11.0) | 6 | 1 | 7.5 | (0.9–169.0) | 2.31[b] |
| | High | 13 | 17 | 0.8 | (0.4–1.9) | 10 | 11 | 1.0 | (0.4–2.6) | 3 | 4 | 0.9 | (0.2–4.9) | −0.16 |
| | All | 137 | 123 | 1.2 | (0.9–1.7) | 79 | 76 | 1.2 | (0.8–1.7) | 36 | 29 | 1.6 | (0.9–2.8) | 1.63 |
| Chi for trend | | | | 0.86 | | | | | | | | | | |
| Chloroform | Unexposed | 257 | 272 | 1.0 | | | | | | | | | | |
| | Low | 30 | 39 | 0.8 | (0.5–1.4) | 16 | 25 | 0.7 | (0.3–1.4) | 8 | 7 | 1.4 | (0.4–4.4) | −0.25 |
| | Medium | 12 | 4 | 3.2 | (0.9–12.0) | 6 | 3 | 2.2 | (0.5–11.3) | 6 | 0 | ∞ | | 2.63[b] |
| | High | 1 | 5 | 0.2 | (0.0–1.8) | 1 | 4 | 0.2 | (0.0–2.2) | 0 | 0 | — | — | −1.43 |
| | All | 46 | 44 | 1.0 | (0.6–1.6) | 23 | 32 | 0.8 | (0.4–1.4) | 14 | 7 | 2.3 | (0.8–6.6) | 0.83 |
| Chi for trend | | | | −0.02 | | | | | | | | | | |
| Methylene | Unexposed | 181 | 212 | 1.0 | | | | | | | | | | |
| chloride | Low | 71 | 77 | 1.0 | (0.7–1.6) | 49 | 56 | 1.0 | (0.6–1.6) | 12 | 12 | 1.2 | (0.5–3.0) | 0.09 |
| | Medium | 29 | 21 | 1.6 | (0.8–3.0) | 22 | 16 | 1.5 | (0.7–3.2) | 4 | 3 | 1.5 | (0.3–9.0) | 1.23 |
| | High | 19 | 10 | 2.4 | (1.0–5.9) | 9 | 6 | 1.8 | (0.6–6.0) | 8 | 2 | 6.1 | (1.1–43.8) | 2.58[b] |
| | All | 119 | 108 | 1.3 | (0.9–1.8) | 80 | 78 | 1.2 | (0.8–1.7) | 24 | 17 | 1.7 | (0.9–3.6) | 1.56 |
| Chi for trend | | | | 2.29[a] | | | | | | | | | | |
| Methyl | Unexposed | 188 | 219 | 1.0 | | | | | | | | | | |
| chloroform | Low | 97 | 93 | 1.2 | (0.8–1.7) | 53 | 57 | 1.0 | (0.6–1.6) | 35 | 23 | 1.8 | (1.0–3.4) | 1.72[a] |
| | Medium | 11 | 5 | 2.2 | (0.7–7.6) | 7 | 3 | 2.4 | (0.5–12.3) | 2 | 2 | 0.9 | (0.1–9.5) | 0.74 |
| | High | 4 | 3 | 1.2 | (0.2–7.3) | 3 | 3 | 0.9 | (0.1–6.0) | 1 | 0 | ∞ | | 0.52 |
| | All | 112 | 101 | 1.2 | (0.9–1.8) | 63 | 63 | 1.1 | (0.7–1.7) | 38 | 25 | 1.8 | (1.0–3.3) | 1.87[a] |
| Chi for trend | | | | 1.48 | | | | | | | | | | |
| Tetrachloro- | Unexposed | 189 | 214 | 1.0 | | | | | | | | | | |
| ethylene | Low | 72 | 63 | 1.3 | (0.8–1.9) | 50 | 48 | 1.1 | (0.7–1.8) | 14 | 11 | 1.6 | (0.6–4.0) | 1.10 |
| | Medium | 30 | 35 | 0.9 | (0.5–1.6) | 15 | 17 | 0.9 | (0.4–1.9) | 11 | 12 | 1.0 | (0.4–2.6) | −0.17 |
| | High | 9 | 8 | 1.2 | (0.4–3.5) | 6 | 6 | 1.0 | (0.3–3.7) | 3 | 0 | ∞ | | 1.32 |
| | All | 111 | 106 | 1.2 | (0.8–1.6) | 71 | 71 | 1.1 | (0.7–1.6) | 28 | 23 | 1.4 | (0.7–2.7) | 1.01 |
| Chi for trend | | | | 0.44 | | | | | | | | | | |
| Trichloro- | Unexposed | 179 | 201 | 1.0 | | | | | | | | | | |
| ethylene | Low | 67 | 66 | 1.1 | (0.7–1.7) | 40 | 41 | 1.0 | (0.6–1.7) | 17 | 16 | 1.3 | (0.6–3.0) | 0.68 |
| | Medium | 42 | 41 | 1.1 | (0.6–1.8) | 24 | 20 | 1.2 | (0.6–2.4) | 14 | 14 | 1.1 | (0.5–2.5) | 0.36 |
| | High | 12 | 12 | 1.1 | (0.5–2.8) | 7 | 7 | 1.1 | (0.3–3.7) | 5 | 1 | 6.1 | (0.7–143.5) | 1.55 |
| | All | 128 | 125 | 1.1 | (0.8–1.6) | 71 | 68 | 1.1 | (0.7–1.7) | 36 | 31 | 1.3 | (0.8–2.3) | 1.03 |
| Chi for trend | | | | 0.45 | | | | | | | | | | |

*For each substance, referent group is composed of those unexposed to the given substance. CAH = chlorinated aliphatic hydrocarbons; ca = cases; co = controls; OR = odds ratio; CI = confidence interval.

[a]$p < 0.05$.

[b]$p < 0.01$.

**TABLE II. Risk of Astrocytic Brain Cancer by Probability and Cumulative Exposure to Organic Solvents and Six CAHs, Controlling for Age and Study Area***

| | | Cumulative exposure score | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Low | | | | Medium | | | | High | | | | |
| CAH | Probability | ca | co | OR | 95% CI | ca | co | OR | 95% CI | ca | co | OR | 95% CI | Chi for trend |
| Organic solvents | Low | 20 | 22 | 1.0 | (0.5–2.1) | 19 | 15 | 1.6 | (0.7–3.7) | 5 | 6 | 1.4 | (0.3–5.6) | 1.30 |
| | Medium | 4 | 8 | 0.6 | (0.1–2.2) | 16 | 12 | 1.7 | (0.7–4.2) | 11 | 5 | 3.1 | (0.9–11.0) | 2.08[a] |
| | High | 15 | 13 | 1.4 | (0.6–3.4) | 32 | 36 | 1.1 | (0.6–1.9) | 45 | 37 | 1.5 | (0.9–2.6) | 1.43 |
| | All | 39 | 43 | 1.0 | (0.6–1.8) | 67 | 63 | 1.3 | (0.8–2.1) | 61 | 48 | 1.7 | (1.0–2.7) | 2.30[a] |
| Carbon tetrachloride | Low | 35 | 34 | 1.1 | (0.6–1.9) | 39 | 36 | 1.3 | (0.8–2.3) | 16 | 16 | 1.3 | (0.6–2.8) | 1.11 |
| | Medium | 1 | 2 | 0.4 | (0.0–6.7) | 7 | 1 | 8.1 | (1.0–178.7) | 4 | 1 | 4.7 | (0.5–114.8) | 2.40[b] |
| | High | 6 | 9 | 0.7 | (0.2–2.2) | 3 | 4 | 0.8 | (0.1–4.4) | 4 | 2 | 2.7 | (0.4–22.1) | 0.43 |
| | All | 42 | 45 | 1.0 | (0.6–1.6) | 49 | 41 | 1.4 | (0.9–2.4) | 24 | 19 | 1.6 | (0.8–3.2) | 1.79[a] |
| Chloroform | Low | 11 | 19 | 0.6 | (0.3–1.4) | 12 | 9 | 1.6 | (0.6–4.2) | 1 | 4 | 0.4 | (0.0–3.6) | −0.37 |
| | Medium | 3 | 2 | 1.6 | (0.2–14.2) | 4 | 1 | 4.7 | (0.5–112.6) | 5 | 0 | ∞ | | 2.63[b] |
| | High | 1 | 0 | ∞ | | 0 | 4 | — | — | 0 | 0 | — | — | −1.79 |
| | All | 15 | 21 | 0.8 | (0.4–1.6) | 16 | 14 | 1.3 | (0.6–2.9) | 6 | 4 | 1.8 | (0.4–7.8) | 0.67 |
| Methylene chloride | Low | 24 | 37 | 0.7 | (0.4–1.3) | 29 | 20 | 1.6 | (0.8–3.0) | 8 | 11 | 0.9 | (0.3–2.5) | 0.39 |
| | Medium | 9 | 8 | 1.3 | (0.4–3.8) | 13 | 6 | 2.3 | (0.8–7.0) | 4 | 5 | 0.9 | (0.2–4.0) | 1.12 |
| | High | 4 | 2 | 2.0 | (0.3–16.7) | 6 | 2 | 4.2 | (0.7–31.4) | 7 | 4 | 2.5 | (0.6–11.0) | 2.18[a] |
| | All | 37 | 47 | 0.9 | (0.5–1.5) | 48 | 28 | 1.9 | (1.1–3.2) | 19 | 20 | 1.2 | (0.6–2.5) | 1.64 |
| Methyl chloroform | Low | 32 | 36 | 1.0 | (0.6–1.7) | 37 | 29 | 1.5 | (0.8–2.6) | 19 | 15 | 1.5 | (0.7–3.2) | 1.46 |
| | Medium | 1 | 1 | 1.0 | (0.0–36.3) | 7 | 2 | 3.6 | (0.7–25.9) | 1 | 2 | 0.5 | (0.0–7.1) | 0.85 |
| | High | 1 | 0 | ∞ | | 3 | 2 | 1.3 | (0.2–12.1) | 0 | 1 | — | — | −0.13 |
| | All | 34 | 37 | 1.0 | (0.6–1.8) | 47 | 33 | 1.6 | (1.0–2.7) | 20 | 18 | 1.3 | (0.6–2.6) | 1.54 |
| Tetrachloro-ethylene | Low | 25 | 31 | 0.8 | (0.4–1.5) | 27 | 19 | 1.6 | (0.8–3.1) | 12 | 9 | 1.8 | (0.7–5.1) | 1.55 |
| | Medium | 7 | 7 | 1.0 | (0.3–3.1) | 13 | 14 | 1.0 | (0.4–2.4) | 6 | 8 | 0.8 | (0.2–2.6) | −0.34 |
| | High | 1 | 2 | 0.5 | (0.0–7.4) | 5 | 4 | 1.2 | (0.3–5.4) | 3 | 0 | ∞ | | 1.37 |
| | All | 33 | 40 | 0.8 | (0.5–1.4) | 45 | 37 | 1.3 | (0.8–2.2) | 21 | 17 | 1.5 | (0.7–3.2) | 1.35 |
| Trichloro-ethylene | Low | 23 | 23 | 1.0 | (0.5–2.0) | 23 | 22 | 1.1 | (0.6–2.3) | 11 | 12 | 1.2 | (0.5–3.0) | 0.52 |
| | Medium | 6 | 11 | 0.5 | (0.2–1.7) | 22 | 14 | 1.6 | (0.8–3.5) | 10 | 9 | 1.1 | (0.4–3.1) | 0.82 |
| | High | 1 | 1 | 1.3 | (0.0–50.6) | 6 | 5 | 1.3 | (0.3–5.0) | 5 | 2 | 3.1 | (0.5–24.4) | 1.31 |
| | All | 30 | 35 | 0.9 | (0.5–1.6) | 51 | 41 | 1.3 | (0.8–2.2) | 26 | 23 | 1.3 | (0.7–2.5) | 1.20 |

*For each CAH, referent group is composed of those unexposed to the given CAH. CAH = chlorinated aliphatic hydrocarbons; ca = cases; co = controls; OR = odds ratio; CI = confidence interval.
[a] $p < 0.05$.
[b] $p < 0.01$.

2–20 years, OR = 1.2 [95% CI: 0.7–1.9]; 21+ years, OR = 3.1 [1.3–7.4], p = .009).

Astrocytic brain tumor risk increased significantly with cumulative exposure scores for organic solvents and for carbon tetrachloride (Table II), chiefly due to increases among those with medium probability of exposure. Among those with high probability of exposure to methylene chloride, the test for trend was statistically significant, although risk did not increase monotonically with cumulative exposure. For chloroform, a significantly increasing trend was observed in the medium probability group only.

Relative risks and trends by cumulative exposure in analyses with a 10-year lag were similar to the results in Table II (data not shown). Lagging exposure by 20 years reinforced ORs and the trends for organic solvents, especially in men with the highest probability of exposure (low cumulative score: OR = 1.1 [95% CI: 0.5–2.3]; medium: OR = 1.4 [0.8–2.5], high: OR = 2.2 [95% CI: 1.0–4.5]; p for trend = .02).

**TABLE III. Risk of Astrocytic Brain Cancer by Average Intensity and Duration of Exposure, Controlling for Age and Study Area***

| | | Duration of employment in exposed jobs | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2–20 years | | | | 21+ years | | | | Total | | | |
| Substance | Average intensity[a] | ca | co | OR | 95% CI | ca | co | OR | 95% CI | ca | co | OR | 95% CI |
| Organic solvents | Low-medium | 62 | 69 | 1.1 | (0.7–1.7) | 64 | 51 | 1.7 | (1.1–2.8) | 126 | 120 | 1.3 | (0.9–1.9) |
| | High | 18 | 16 | 1.4 | (0.6–3.1) | 23 | 18 | 1.6 | (0.8–3.4) | 41 | 34 | 1.5 | (0.9–2.7) |
| Chi for trend | | | | 0.85 | | | | 2.15[b] | | | | 1.85[b] | |
| Carbon tetrachloride | Low-medium | 65 | 70 | 1.0 | (0.7–1.6) | 28 | 26 | 1.4 | (0.7–2.6) | 93 | 96 | 1.1 | (0.8–1.6) |
| | High | 14 | 6 | 2.8 | (1.0–8.5) | 8 | 3 | 3.1 | (0.7–15.3) | 22 | 9 | 2.9 | (1.2–7.1) |
| Chi for trend | | | | 1.35 | | | | 1.90[b] | | | | 2.06[b] | |
| Chloroform | Low-medium | 19 | 27 | 0.8 | (0.4–1.5) | 11 | 7 | 1.9 | (0.6–5.6) | 30 | 34 | 1.0 | (0.6–1.7) |
| | High | 4 | 5 | 0.8 | (0.2–3.6) | 3 | 0 | ∞ | | 7 | 5 | 1.4 | (0.4–5.2) |
| Chi for trend | | | | −0.78 | | | | 2.01[b] | | | | 0.32 | |
| Methylene chloride | Low-medium | 65 | 65 | 1.1 | (0.7–1.7) | 11 | 14 | 0.9 | (0.4–2.2) | 76 | 79 | 1.1 | (0.7–1.6) |
| | High | 15 | 13 | 1.4 | (0.6–3.2) | 13 | 3 | 6.1 | (1.5–28.3) | 28 | 16 | 2.2 | (1.1–4.4) |
| Chi for trend | | | | 0.78 | | | | 2.43[c] | | | | 1.86[b] | |
| Methyl chloroform | Low-medium | 54 | 53 | 1.1 | (0.7–1.8) | 32 | 23 | 1.6 | (0.9–3.1) | 86 | 76 | 1.3 | (0.8–1.9) |
| | High | 9 | 10 | 0.9 | (0.3–2.6) | 6 | 2 | 3.7 | (0.7–27.9) | 15 | 12 | 1.4 | (0.6–3.2) |
| Chi for trend | | | | 0.25 | | | | 2.28[b] | | | | 1.35 | |
| Tetrachloro-ethylene | Low-medium | 64 | 65 | 1.0 | (0.7–1.6) | 25 | 23 | 1.3 | (0.7–2.4) | 89 | 88 | 1.1 | (0.8–1.6) |
| | High | 7 | 6 | 1.2 | (0.4–4.4) | 3 | 0 | ∞ | | 10 | 6 | 1.8 | (0.6–5.9) |
| Chi for trend | | | | 0.42 | | | | 1.47 | | | | 1.04 | |
| Trichloro-ethylene | Low-medium | 52 | 52 | 1.1 | (0.7–1.7) | 27 | 25 | 1.2 | (0.6–2.3) | 79 | 77 | 1.1 | (0.7–1.7) |
| | High | 19 | 16 | 1.2 | (0.6–2.7) | 9 | 6 | 1.8 | (0.6–6.1) | 28 | 22 | 1.4 | (0.7–2.6) |
| Chi for trend | | | | 0.57 | | | | 1.21 | | | | 1.02 | |

*For each substance, referent group is composed of those unexposed to the given substance. ca = cases; co = controls; OR = odds ratio; CI = confidence interval.
[a]Based on the original intensity scores of low = 1, medium = 2, and high = 3. For this analysis, low-medium was average intensity of 1–2; high was average intensity >2. Intensity of exposure was averaged and duration summed over all exposed jobs for each subject, regardless of probability.
[b]$p < 0.05$.
[c]$p < 0.01$.

For individual CAHs, relatively few study subjects attained high cumulative scores after lagging by 20 years.

For organic solvents and all six CAHs, risks tended to increase with employment in jobs judged to have higher average intensity, particularly among men employed more than 20 years in such jobs, grouping all probabilities (Table III). The increases with intensity for longer-held jobs were statistically significant for all but tetrachloroethylene and trichloroethylene. Similar patterns were observed when the analysis was restricted to men with high probability of exposure, except for chloroform and methyl chloroform (not shown). Risk estimates were elevated but unstable for 21 or more years at high average intensity for carbon tetrachloride (two cases, no controls), methylene chloride (OR = 12.0, 95% CI = 1.4–265.5; eight cases), tetrachloroethylene (two cases, no controls), and trichloroethylene (OR = 5.1, 95% CI = 0.5–125.0; four cases). For men with high probability of exposure to the other two solvents, risks did not increase with intensity, and no subjects were employed in high intensity jobs for 21 or more years.

**TABLE IV. Risk of Astrocytic Brain Cancer by Probability of Exposure, Controlling for Age, Study Area, Employment in Electronics Occupations/Industries, and Exposure to Other CAHs by Logistic Regression***

| | Probability of exposure to agent[a] | | | | | | |
|---|---|---|---|---|---|---|---|
| | Low | | Medium | | High | | Chi for |
| Agent | OR | 95% CI | OR | 95% CI | OR | 95% CI | trend |
| Carbon tetrachloride | 1.3 | (0.8–2.1) | 2.2 | (0.6–8.1) | 0.6 | (0.2–1.7) | −0.25 |
| Methylene chloride | 0.9 | (0.5–1.6) | 1.4 | (0.6–3.1) | 2.4 | (0.9–6.4) | 2.08[b] |
| Tetrachloroethylene | 1.0 | (0.5–1.8) | 0.5 | (0.2–1.3) | 1.2 | (0.4–3.9) | −0.65 |
| Trichloroethylene | 0.9 | (0.5–1.8) | 1.5 | (0.6–3.4) | 1.0 | (0.3–3.1) | −0.11 |

*CAH = chlorinated aliphatic hydrocarbons; OR = odds ratio; CI = confidence interval.
[a]Adjusted for age, study area, and employment in electronics-related occupations or industries, and probability of exposure to three other solvents listed.
[b]$p < .05$.

Risks calculated for specific categories of intensity of exposure (not shown)—e.g., high intensity, medium but never high—rose less smoothly than those calculated for average intensity, but were consistent with the results in Table III. For all probabilities combined, for all six CAHs and organic solvents, brain tumor risks tended to be higher for subjects in jobs with high intensity compared to medium or low, and with longer employment at any intensity. Few men were employed more than 20 years in jobs rated as high probability and high intensity of exposure to an individual CAH. Among those with more than 20 years at high intensity, the association with brain cancer was strongest, and rose with probability, for carbon tetrachloride (all probabilities: OR = 1.8, 95% CI = 0.7–4.6; high probability: two cases, no controls), methylene chloride (all probabilities: OR = 6.7, 95% CI = 1.3–47.4; high probability: OR = 8.8, 95% CI = 1.0–200.0), and trichloroethylene (all probabilities: OR = 5.1, 95% CI = 0.9–36.7; high probability: four cases, no controls).

Many subjects were assigned exposure to more than one CAH, sometimes even in the same job. We therefore attempted to separate the effects of the four CAHs that showed the most evidence of an association with brain cancer in the analyses presented above. Logistic regression was used to evaluate simultaneously the effects of methylene chloride, carbon tetrachloride, tetrachloroethylene, and trichloroethylene, controlling for age, study area, and employment in electronics-related occupations or industries (Table IV). Risk of astrocytic brain tumor increased significantly with probability to over twofold among those exposed to methylene chloride, controlling for exposure to the other solvents. In analyses which omitted the 30 subjects with electronics-related jobs, results were essentially the same as those presented.

Duration at high probability was difficult to evaluate by logistic regression; models yielded infinite risks for tetrachloroethylene, and uninterpretable coefficients for any other CAH analyzed simultaneously. In analyses for carbon tetrachloride, methylene chloride, or trichloroethylene, considered two at a time, risks were threefold or higher for high probability of more than 20 years' exposure to methylene chloride or trichloroethylene, and were less than one for carbon tetrachloride, but none was statistically significant. In analyses of intensity and duration, adjustment for exposure to the other agents increased risks associated with methylene chloride, but not with the other CAHs (Table V). Considering all probabilities, subjects employed

**TABLE V. Risk of Astrocytic Brain Cancer by Intensity of Exposure and Duration of Employment in Exposed Jobs, Controlling for Age, Study Area, Employment in Electronics Occupations/Industries, and Exposure to Other CAHs by Logistic Regression***

| Agent | Average intensity of exposure | Duration of employment in exposed jobs[a] | | | | Chi for trend |
|---|---|---|---|---|---|---|
| | | 2–20 years | | 21+ years | | |
| | | OR | 95% CI | OR | 95% CI | |
| Carbon tetrachloride | Low-medium | 0.9 | (0.5–1.6) | 1.3 | (0.6–2.9) | |
| | High | 2.9 | (0.8–10.9) | 1.0 | (0.2–7.3) | |
| | Chi for trend | | 0.83 | | 0.67 | |
| | Total | 1.0 | (0.6–1.7) | 1.1 | (0.5–2.5) | 0.50 |
| Methylene chloride | Low-medium | 1.0 | (0.5–1.9) | 1.3 | (0.4–3.8) | |
| | High | 1.3 | (0.5–3.7) | 8.5 | (1.3–55.5) | |
| | Chi for trend | | 0.33 | | 1.97[b] | |
| | Total | 1.0 | (0.6–1.8) | 1.9 | (0.7–5.2) | 0.67 |
| Tetrachloroethylene | Low-medium | 0.9 | (0.4–1.7) | 0.8 | (0.3–2.5) | |
| | High | 1.1 | (0.2–5.5) | ∞ | — | |
| | Chi for trend | | 0.45 | | 0.65 | |
| | Total | 0.8 | (0.4–1.6) | 1.1 | (0.4–3.1) | −0.15 |
| Trichloroethylene | Low-medium | 1.2 | (0.6–2.5) | 1.1 | (0.4–2.9) | |
| | High | 0.9 | (0.3–2.3) | 0.2 | (0.0–1.3) | |
| | Chi for trend | | 0.02 | | −1.14 | |
| | Total | 1.1 | (0.6–2.3) | 0.8 | (0.3–2.1) | −0.14 |

*CAH = chlorinated aliphatic hydrocarbons; OR = odds ratio; CI = confidence interval.
[a]Adjusted for age, study area, employment in electronics-related occupations or industries, and for duration and intensity of exposure to three other solvents listed.
[b]$p < 0.05$.

more than 20 years in jobs with high average intensity of exposure to methylene chloride experienced an over eightfold excess of brain cancer.

## DISCUSSION

We attempted to evaluate separately the relationship between several CAHs and risk of astrocytic brain cancer, using several surrogates of exposure. These included employment in jobs (occupation/industry combinations) thought to entail exposure, duration of employment in exposed jobs, probability and average intensity of exposure in those jobs, and a cumulative exposure score. The strongest association was with methylene chloride, for which relative risks rose with probability, duration, and average intensity of exposure, although not with the cumulative exposure score. Adjustment for exposure to the other CAHs did not diminish the association. Estimated risks rose as high as eightfold with 21 or more years of exposure at high intensity, adjusting for exposure to the other CAHs. Carbon tetrachloride, tetrachloroethylene, and trichloroethylene also showed some indication of increasing risk with duration, the cumulative exposure score, and average intensity, but risks were smaller and trends were less consistent than for methylene chloride. The patterns for methylene chloride, carbon tetrachloride, tetrachloroethylene, and trichloroethylene warrant future attention. In contrast, exposure to chloroform or methyl chloroform

showed little indication of an association with brain cancer; risk increases were observed almost exclusively among the low and medium probability groups.

Associations between brain cancer and organic solvents have been reported previously [Thomas and Waxweiler, 1986; Cordier et al., 1988; Park et al., 1990]. These findings are unique in that risks for the individual chemicals, carbon tetrachloride, methylene chloride, tetrachloroethylene, and trichloroethylene, were at least as high or higher than risks for the general category of organic solvents, although CIs were wide and overlapping. Associations with carbon tetrachloride and trichloroethylene appeared to be explained in part by exposure to tetrachloroethylene and/or methylene chloride. In contrast, associations with probability and intensity of exposure to methylene chloride persisted after adjusting for the other solvents. For tetrachloroethylene, associations were not as consistent, but risk remained elevated in the highest intensity and duration group after adjusting for the other solvents, based on three cases and no controls.

The susceptibility of glial cells, of which astrocytes are a subset, to environmental carcinogens is plausible because of their transport function and their ability to replicate [Glees, 1988]. CAHs can pass the blood-brain barrier because of their high solubility in fats [Sato and Nakajima 1979a,b]. CAHs demonstrate central nervous system effects [Putz et al., 1976; Waters et al., 1977; Haley and Berndt, 1987], although symptoms immediately following methylene chloride exposure are probably due in large part to carbon monoxide, a major metabolite [Putz et al., 1976].

Evidence for the carcinogenicity of these CAHs comes primarily from animal studies and is sufficient for carbon tetrachloride, methylene chloride, and tetrachloroethylene (in organs other than brain) and limited for trichloroethylene [IARC, 1987]. The chlorinated hydrocarbons vinyl chloride and bis-(chloromethyl)ether are animal brain carcinogens [IARC, 1987; Maltoni et al., 1982].

Two epidemiologic studies suggest associations of chlorinated hydrocarbons with brain cancer. Chlorinated hydrocarbons and chlorofluorocarbons were strongly associated with brain cancer mortality among workers at a plant which manufactured missile and aircraft guidance systems; risks were highest among those with the highest cumulative exposure [Park et al., 1990]. Brain cancer mortality was positively correlated with the concentration of halomethanes in drinking water for 76 U.S. counties [Cantor et al., 1978]. However, evidence for the carcinogenicity of these six specific CAHs is inadequate in humans, as noted recently by IARC [1979, 1986, 1987]. No excess of brain cancer has been observed in two cohorts of workers exposed to methylene chloride: one in the manufacture of cellulose triacetate (numbers not reported [Lanes et al., 1990]) and the other in photographic film manufacture [Hearne et al., 1987, 1990] (O/E [observed/expected] = 2/1.7 in the most recent followup [Hearne et al., 1990]). Tetrachloroethylene is widely used as a dry cleaning solvent and several investigations have evaluated mortality risks of workers in this industry [Blair et al., 1990; Norman and Fraumeni, 1981; Duh and Asal, 1984; Katz and Jowett, 1981; Brown and Kaplan, 1987; Lin and Kessler, 1981; Stemhagen et al., 1983; Hernberg et al., 1984; Silverman et al., 1989]. Excesses have been noted for several cancer sites, but not the brain. The largest cohort study of dry cleaners to date had a deficit of brain cancer (1 observed vs. 4.6 expected) [Blair et al., 1990]. Excesses of gynecologic and breast, but not brain, cancers were reported among women potentially exposed to trichloroethylene and methylene chloride in lamp manufacturing [Shannon et al., 1988]. A cohort study of workers at an aircraft maintenance facility found

excesses of other cancers but not central nervous system cancer, among men (9 observed, 10.1 expected) or women (none observed, 1.4 expected) exposed to trichloroethylene [Spirtas et al., 1991]. In that study, carbon tetrachloride and tetrachloroethylene were associated with non-Hodgkin's lymphoma, but risks were not reported for brain cancer [Spirtas et al., 1991]. No other epidemiologic studies specifically focusing on cancer risks from exposure to carbon tetrachloride are available from the literature [IARC, 1987]. Most of the available cohort studies are too small to be likely to detect moderate increases in risk of a rare disease like brain cancer [Axelson, 1980; Hearne et al., 1987, 1990; Lanes et al., 1990; Norman and Fraumeni, 1981; Duh and Asal, 1984; Katz and Jowett, 1981; Brown and Kaplan, 1987; Lin and Kessler, 1981; Stemhagen et al., 1983; Hernberg et al., 1984; Silverman et al., 1989].

The principal limitation of our study is the lack of direct information on exposure to solvents. Judgments regarding exposure made by industrial hygienists were based on work histories provided by next-of-kin, who are likely to provide less accurate information than subjects themselves or workplace records [Lerchen and Samet, 1986; Coggon et al., 1985]. Poor specificity of some work histories for specific solvents and the interchangeability of solvents for many applications probably reduced the accuracy of exposure assignments. Exposure to solvents is difficult to assess under the best circumstances, given changing patterns and multiple or mixed uses in many occupations and industries.

These limitations undoubtedly resulted in misclassification of individuals according to any of our measures of exposure to the solvents. However, the sources of potential error do not appear likely to have significantly biased risk estimates away from the null or to have created the observed trends [Wacholder et al., 1991]. The industrial hygienists made their exposure assignments without knowledge of the case/control status of the subjects. Over a third of the next-of-kin of eligible cases and controls were not interviewed. This limitation, however, could spuriously create the observed associations only by underrepresenting cases who were unexposed, and/or controls who were exposed, to solvents in general, and methylene chloride in particular. Differential recall bias was unlikely since occupational histories came from next-of-kin of both cases and controls. No associations were observed between brain cancer and exposure to chloroform or methyl chloroform, so if differential misclassification occurred, it had to affect only some of the chemicals. In the face of these limitations, the consistency of exposure-response trends for methylene chloride was surprising and suggestive.

Few individual risks were statistically significant and most CIs were broad. Although numerous statistical tests were conducted, our interpretation of these results is based not on isolated significant findings, but on patterns of trends. While the role of chance cannot be totally dismissed, the trends and consistency of the methylene chloride and brain cancer associations suggest that chance seems unlikely to entirely explain the results.

Men judged to have high probability of exposure to methylene chloride were employed in painting; paint or varnish manufacture; ship or boat building and repair; and electronics manufacture. Those with high-intensity exposure included those high-probability subjects plus others employed in the roofing and the pharmaceutical industry. The high cumulative/high probability exposure category consisted of subjects whose longest-held exposed job was judged to be both high duration and high intensity. No paint strippers, an occupation known to have high exposures to meth-

ylene chloride, were found among cases and controls. However, the matrix was designed to be sensitive, and it is not unusual in a population-based study to have no subjects representing a rare occupation. Subjects assigned high probability and intensity of tetrachloroethylene exposure were dry cleaners. A jewelry worker was also assigned high probability but low level of exposure to tetrachloroethylene. We were unable to identify any other specific exposures common to the jobs considered exposed that might explain the observed associations.

In summary, application of a job exposure matrix for six chlorinated aliphatic hydrocarbon (CAH) solvents to a case-control study of astrocytic brain cancer noted an association with employment in jobs with potential exposure to methylene chloride. Risks increased significantly with several measures of exposure, including probability, average intensity, and duration of employment, although not with a cumulative exposure score. Associations of tetrachloroethylene, trichloroethylene, and carbon tetrachloride with brain cancer may have been confounded by exposure to methylene chloride. As the first evidence of such an association, these results should be interpreted cautiously. If these agents are not in themselves brain carcinogens, they may be particularly good markers of a class of solvents or a specific combination of solvents that together act to increase risk of brain cancer. Specific chlorinated hydrocarbons, perhaps especially methylene chloride, should be evaluated in future studies of astrocytic brain cancer.

## ACKNOWLEDGMENTS

The authors acknowledge the valuable contributions of the following cooperating institutions and individuals: Louisiana State University, New Orleans, LA—Dr. Elizabeth T.H. Fontham, Dr. Pelayo Correa; University of Pennsylvania School of Medicine, Philadelphia, PA—Dr. Sandra A. Norman, Dr. Paul D. Stolley, Ms. Margaret Dunn; and New Jersey State Department of Health—Dr. Annette Stemhagen. The authors also thank John Friedbauer for excellent programming support.

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